Novel Combination Therapy for Schizophrenia Focused on Improved Cognition: 5-HT-2A/D2 Blockade with Adjunctive Blockade of Prefrontal DA Reuptake

This application claims the benefit of priority of United States Provisional Application Number 60/421,980 filed on October 29, 2002.

FIELD OF THE INVENTION

The invention involves the fields of medical and pharmaceutical sciences. The invention further involves the treatment of medical conditions using a combination of pharmaceutical compounds. In particular, the invention involves the treatment of the symptoms associated with schizophrenia.

BACKGROUND OF THE INVENTION

Schizophrenia, as used herein, refers to schizophrenia, cognitive dysfunction schizophrenia, and schizoaffective disorder. Different types of schizophrenia include (1) paranoid schizophrenia where a subject feels extremely suspicious, persecuted, grandiose, or experiences a combination of these emotions; (2) disorganized schizophrenia where a subject is often incoherent but may not have delusions; (3) catatonic schizophrenia where a subject is withdrawn, mute, negative and often assumes very unusual postures; and (4) residual schizophrenia where a person is no longer delusion or hallucinating, but has no motivation or interest in life. Symptoms of schizophrenia include delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms such as affective flattening, alogia, and avolition. See American Psychiatric Association. (1994), Diagnostic and statistical manual of mental disorders, fourth edition. Washington, DC: American Psychiatric Association. In recent years, it has been recognized that cognitive dysfunction is a third major diagnostic category for schizophrenia which is difficult to treat with the most consistently observed deficit, working memory.

Symptoms of schizoaffective disorder include major depressive episode, manic episode, mixed episode, delusions, hallucinations, disorganized speech (e.g., frequent derailment or

incoherence), grossly disorganized or catatonic behavior, and negative symptoms (e.g., affective flattening, alogia, avolition). See *id.*

Since the inception of typical antipsychotic drug therapies for the amelioration of the symptoms of schizophrenia, there has been little progress in developing new drugs that are as efficacious in treating the cognitive deficits that characterize the illness and lead to devastating socioeconomic difficulties as they are in treating the positive and negative symptoms. All currently known antipsychotics are substantially equally effective in treating positive symptoms with some of the atypical antipsychotics having some efficacy for negative symptoms but none of the present drugs have significant cognitive benefits.

While the benefits of combinative therapies are well known, such therapies have either not been fully exploited or have not been successfully applied to date in the treatment of schizophrenia. Thus, there is a need in the art for more effective therapies for the treatment of schizophrenia. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

BRIEF SUMMARY OF THE INVENTION

One embodiment of the invention provides a combination comprising a drug that blocks 5-HT-2A receptors, a drug that blocks D2 receptors, and a drug that blocks dopamine reuptake, wherein the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake together comprise a therapeutically effective amount of the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake. The drug that blocks 5-HT-2A receptors can be a 5-HT-2A antagonist. The drug that blocks D2 receptors can be a D2 antagonist. The drug that blocks dopamine reuptake can be a dopamine transporter blocker. The combination can be a single dosage form.

In the combination, one single drug can block 5-HT-2A receptors, block D2 receptors, and blocks dopamine reuptake. In one combination a first drug can block 5-HT-2A receptors and can block D2 receptors, and a second drug can block dopamine reuptake. In one combination a

first drug can block 5-HT-2A receptors and can inhibit dopamine reuptake, and a second drug can block D2 receptors. In one combination a first drug can block D2 receptors and can inhibit dopamine reuptake, and a second drug can block 5-HT-2A receptors.

Another embodiment of the invention provides a method of treating schizophrenia in a subject comprising administration to the subject of a combination comprising a drug that blocks 5-HT-2A receptors, a drug that blocks D2 receptors, and a drug that blocks dopamine reuptake, wherein the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake together comprise a therapeutically effective amount of the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and a the drug that blocks dopamine reuptake. The administration of each of the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake can occur sequentially within about 24, 12, 6, 3 or 1 hours. The administration of each of the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and a the drug that blocks dopamine reuptake can occur substantially concomitantly.

Even another embodiment of the invention provides a method of treating schizophrenia in a subject comprising blocking 5-HT-2A receptors, blocking D2 receptors, and inhibiting dopamine reuptake in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

It is now well recognized that the atypical antipsychotics which block both serotonin 5-HT-2A and dopamine D2 receptors have a marginally better cost-benefit ratio than the typical neuroleptics in terms of treating positive and negative symptoms of schizophrenia with less side effects such as extrapyramidal (movement) disorders. The combinative therapy disclosed herein is inspired by the concept that any real (statistically detected) improvement in cognition, especially working memory can also result in concomitant improvement of certain aspects of positive and negative symptoms. This downstream action of improved cognition is, for instance, is likely to contribute to better social communication and less incoherence of thought

processes. To this end, the invention combines a mechanism of stimulation of dopamine receptors, specifically targeted at prefrontal cortex, with an optimal combination of 5-HT-2A and D2 receptor blockade. To achieve the former component, a selective dopamine reuptake blocker is used that preferentially elevates dopamine concentrations in prefrontal cortex rather striatum.

One aspect of the invention involves a method for improving cognition in a patient or t diagnosed with schizophrenia. Such a method can involve administering to the patient a ceutical composition that blocks 5-HT-2-A receptors, a pharmaceutical composition that bl s D2 receptors, and a pharmaceutical composition that blocks dopamine reuptake. The pharmaceutical composition that blocks 5-HT-2-A receptors in such a method can comprise a 5-HT-2-A antagonist. Also, the pharmaceutical composition that blocks D2 receptors in such a method can comprise a D2 antagonist. Furthermore, the pharmaceutical composition that blocks dopamine reuptake in such a method can comprise a dopamine transporter blocker (reuptake). As used herein, "blocks" means that 5-HT-2-A receptors and/or D2 receptors are made less available to ligands that would normally interact with these receptors. For example, 5-HT-2 receptors and/or D2 receptors are 10%, 25%, 35%, 45%, 50%, 60%, 70%, 80%, 90%, or 95% less available to ligands that would normally interact with the receptors. "Blocks" also means that dopamine reuptake is reduced. For example, dopamine reuptake is reduced by 10%, 25%, 35%, 45%, 50%, 60%, 70%, 80%, 90% or 95%.

As mentioned, atypical anti-psychotics that block both 5HT-2A and D2 receptors have proven to be less than optimal for managing negative symptoms and cognitive dysfunction in subjects with schizophrenia. In addition to the less than optimal treatment, the most preferred atypical anti-psychotics (e.g., Clozapine) also have dangerous side effects, such as extra-pyramidal movement disorders, blood disorders and cardiac side effects.

The invention provides a combination drug therapy for subjects with schizophrenia. The therapy can comprise an optimal combination of a 5-HT-2A antagonist, a D2 antagonist

and a dopamine inhibitor. This therapy is designed to provide stimulation of dopamine receptors through, for example, a selective dopamine reuptake blocker that preferentially elevates extracellular dopamine concentrations in prefrontal cortex rather than the striatum as a means of improving cognition including working memory while providing relief from positive symptoms associated with the disease and improved treatment of negative symptoms.

One embodiment of the invention provides a combination drug therapy for subjects with schizophrenia. Schizophrenia, as used herein, refers to schizophrenia, cognitive dysfunctional schizophrenia, and schizoaffective disorder. The therapy can comprise an optimal combination comprising a first amount of a drug that blocks 5-HT-2A receptors, a second amount of a drug that blocks D2 receptors, and a third amount of a drug that blocks dopamine reuptake, wherein the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake together comprise a therapeutically effective composition.

Compounds of the Invention

Drugs that Block 5-HT-2A Receptors

A drug that blocks 5-HT-2A receptors can be, for example a 5-HT-2A antagonist. Examples of drugs that block 5-HT-2A receptors include olanzapine, risperidone, ziprasidone, pizotifen, risperidone, iloperidone, ritanserin, ketanserin, cyproheptadine, aripiprazole, arylipiperazines, risperidone metabs (Sepracor), ACP-103 (ACADIA), AT-1015 (Ajinomoto), Org-5222 (Akzo Nobel), AR-116081 (Arena), MDL-100907 (Aventis), Pharmaprojects No. 2865 (Aventis), RP 71602 (Aventis), IT-657 (Bristol-Myers Squibb), F-94116-CN (Faes), GMC-283 (Merck KGaA), and Pharmaprojects No. 5350 (Servier), and pharmaceutically acceptable salts thereof. See Pharmaprojects, August 2002, PJB Publications Ltd.

Drugs that Block D2 Receptors

A drug that blocks D2 receptors can be, for example, a D2 antagonist. Drugs that block D2 receptors can include, for example, tiapride, sultopride, melperone, carpipramine, bromperidol, pimozide, timiperone, quetiapine fumarate, blonanserin, olanzapine,

zuclopenthixol, zuclopenthixol acetate, raclopride, haloperidol, remonpride, sulpiride, Y-931 (Mitsubishi Pharma), risperidone, ziprasidone, and iloperidone. See Pharmaprojects, August 2002, PJB Publications Ltd.

Drugs that Inhibit Dopamine Reuptake

Drugs that inhibit dopamine reuptake can be, for example, dopamine transporter blockers. Drugs that inhibit dopamine reuptake include, for example, brasofensine, GW-320659 (GlaxoSmithKline), GW-353162 (GlaxoSmithKline), ALE-26018 (Johnson Matthey), ATI-61X (Cobrex) (Addiction Therapies), GYKI-52895 (Gedeon Richter), GBR-12909 (Novo Nordisk), diclofensine, lithium and pharmaceutically acceptable salts thereof. See Pharmaprojects, August 2002, PJB Publications Ltd.

Combinations of Compounds of the Invention

One or more drugs that block 5-HT-2A receptors can be combined with one or more drugs that block D2 receptors, and with one or more drugs that inhibit dopamine reuptake in a combinative therapy, for example, in a single dosage form or in separate dosage forms to be administered sequentially.

In the combination, one single drug can block 5-HT-2A receptors, block D2 receptors, and blocks dopamine reuptake. In one combination a first drug can block 5-HT-2A receptors and can block D2 receptors, and a second drug can block dopamine reuptake. In another combination a first drug can block 5-HT-2A receptors and can inhibit dopamine reuptake, and a second drug can block D2 receptors. In yet another combination a first drug can block D2 receptors and can inhibit dopamine reuptake, and a second drug can block 5-HT-2A receptors.

Methods of Treating Schizophrenia

The invention provides methods of treating schizophrenia in a subject comprising blocking 5-HT-2A receptors, blocking D2 receptors, and inhibiting dopamine reuptake in a subject in need thereof. Combination therapy, as used herein, is the administration of one or

more drugs that block 5-HT-2A receptors, one or more drugs that block D2 receptors and one or more drugs that inhibit dopamine reuptake sequentially, substantially sequentially, and/or concomitantly in a regimen that will provide beneficial effects of the drug combination. The drugs that block 5-HT-2A receptors, the drugs that block D2 receptors, and the drugs that inhibit dopamine reuptake are present in therapeutically effective amounts. That is, they are present in amounts that will achieve the goal of treatment of schizophrenia. The combination therapy is also useful with adjunctive therapies. For example, the combination therapy of the invention can be used in combination with other drugs useful in the treatment of schizophrenia.

The invention provides a method of treating schizophrenia in a subject comprising administration to the subject of a combination comprising a first amount of a drug that blocks 5-HT-2A receptors, a second amount of a drug that blocks D2 receptors, and a third amount of a drug that blocks dopamine reuptake, wherein the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake together comprise a therapeutically effective amount of the drugs.

Schizophrenia is treated where one or more symptoms are alleviated or reduced, the disease is prevented and/or the disease occurrence is moderated. Treatment also refers to the slowing of the progression of schizophrenia or prophylactically reducing or inhibiting schizophrenia. Symptoms of schizophrenia include positive symptoms such as delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms such as psychomotor depression, social withdrawal, affective flattening, alogia, and avolition and cognitive deficits, especially in working memory, Wisconsin card slot, planning and smooth pursuit categories.

Each of the doses of the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake can occur within about 24 hours of each other. In other embodiments of the invention each of the doses of the drug that blocks 5-HT-2A receptors, the drug that blocks D2 receptors, and the drug that blocks dopamine reuptake can

occur within about 12, 6, 3, or 1 hours of each other. Preferably, the doses of the drugs are administered substantially concomitantly, for example in a single dosage form.

The combination of one or more drugs that block 5-HT-2A receptors, one or more drugs that block D2 receptors, and one or more drugs that inhibit dopamine reuptake provide greater than expected results in the treatment of schizophrenia, i.e., greater that the sum of each drug's effect taken separately. The results are greater than those that would be expected from the prior art and provide a significant practical advantage in the treatment of schizophrenia. For example, fewer and less severe side effects occur with this treatment than with traditional therapies, including, for instance, fewer extrapyramidal symptoms due to decreasing independent D2 blockade. The compositions and methods of the invention also have greater dosing flexibility and provide cognitive benefits that can be seen quicker than with known compositions and methods.

Administration Methods

The compositions of the invention can be administered to a subject by any means known in the art. A subject can be an animal, such as a mammal, including, for example, humans and non-human primates. The compositions of the invention can be present in a pharmaceutically acceptable formulation or composition. A pharmaceutically acceptable composition or formulation comprises one or more drugs that block 5-HT-2A receptors and/or one or more drugs that block D2 receptors, and/or one or more drugs that inhibit dopamine reuptake, and preferably, an acceptable carrier, such as a stabilizer, buffer, and/or the like. The one or more drugs that block 5-HT-2A receptors and/or one or more drugs that block D2 receptors, and/or one or more drugs that inhibit dopamine reuptake can be administered and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutically acceptable composition or formulation. Pharmaceutically acceptable formulations or compositions treat a disease state, such as schizophrenia, in a subject.

A pharmaceutically acceptable formulation of the invention can allow for the effective distribution of the compositions of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the compositions of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85), which can enhance entry of drugs into the CNS (Jolliet-Riant and Tillement, 1999, *Fundam. Clin. Pharmacol.*, 13, 16-26); biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery after intracerebral implantation (Emerich, DF *et al*, 1999, *Cell Transplant*, 8, 47-58) (Alkermes, Inc. Cambridge, MA); and loaded nanoparticles, such as those made of polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (*Prog Neuropsychopharmacol Biol Psychiatry*, 23, 941-949, 1999).

The present invention also includes pharmaceutically acceptable compositions prepared for storage or administration, which include the desired compounds in a pharmaceutically acceptable carrier, diluent, or adjuvant. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985) hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

A pharmaceutically acceptable composition or formulation is in a form suitable for administration into a cell or subject. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell or organ. For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

A pharmaceutically acceptable formulation of the invention can be delivered to a subject by a liposome delivery mechanism. Standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as for example, tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable or inhalation administration.

The pharmaceutically acceptable formulations can be locally delivered by, for example, injection or by use of an infusion pump. Direct injection, such as subcutaneous, intramuscular, or intradermal injection, can take place using standard needle and syringe methodologies, or by needle-free technologies such as those described in Conry *et al.*, 1999, *Clin. Cancer Res.*, 5, 2330-2337 and Barry *et al.*, International PCT Publication No. WO 99/31262.

Compositions of the invention can be delivered to a subject by systemic administration. Systemic administration is *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that can lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, transdermal, oral, intrapulmonary and intramuscular.

The compositions of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intradermal, intramuscular, or intrathecal injection or infusion techniques and the like.

The pharmaceutical compositions can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical

compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient or ingredients in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example

polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutically acceptable compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This

suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drugs. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compositions can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

A pharmaceutically effective dose is that dose required to treat a disease state such as schizophrenia. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical

characteristics of the specific mammal under consideration, concurrent medication, and other factors that those skilled in the medical arts will recognize.

A drug that blocks 5-HT-2A receptors, a drug that blocks D2 receptors, and a drug that blocks dopamine reuptake can each be present in a dose of about 1 to about 10,000 mg/day, of about 10 to about 10,000 mg/day, of about 25 to about 500 mg/day, of about 50 to about 200 mg/day, or about 0.25 mg to about 50 mg/day. The amount of active ingredient that can be combined with any carrier materials to produce a single dosage form or separate dosage forms varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 10^{-6} to 10^{2} mg/kg/day of an active ingredient.

It is understood that the specific dose level for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

All patents, patent applications, and other scientific or technical writings referred to anywhere herein are incorporated by reference. The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined

by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.